Notice of Allowability	Application No.	Applicant(s)	
	10/055,245	MUTZ ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Interview of 04/23/04*.

2. ☒ The allowed claim(s) is/are *1-12,14,15,19,21,22,25,28,33,38,40-50,52-54,56,57,61,63,64,66,67,70-72,75-86,88-94,96,99,107 and 109-129*.

3. ☒ The drawings filed on *22 January 2002* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *04/23/04* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

1. Amendment and Applicant's Remarks, filed on 03/01/04 are acknowledged.

EXAMINER'S AMENDMENT

2. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Shelley Eberle on 04/23/04.

The application has been amended as follows:

Cancel **claims 130-150** without prejudice.

Cancel **claims 7, 13, 16-18, 20, 23-24, 26-27, 29-32, 34-37, 39, 51, 55, 58-60, 62, 65, 68-69, 73-74, 87, 95, 97-98, 100-106** and **108.**

Amend the following claims:

Claim 1 (Twice amended): A method for generating ~~a fluid volume~~ at least one fluid sample having a volume of no more than about 100 microliters on a substrate, containing a moiety of interest for crystallization and having a known composition, comprising

positioning an acoustic ejector in acoustic coupling relationship with a reservoir of fluid, and

directing acoustic radiation from the ejector into the reservoir, thereby acoustically depositing one or more reagent-containing fluid droplets at a site on the a substrate surface,

wherein at least one of the ejector and the reservoir is movable relative to the other, at least one of the reagent-containing fluid droplets deposited at the site contains the moiety of interest for crystallization, and at least one of the reagent-containing fluid droplets contains an agent that increases the likelihood of crystal formation.

Claim 2 (Amended): The method of claim 1 further comprising a step for detecting whether the moiety of interest for crystallization has formed crystals.

Claim 3 (Twice amended): The method of claim 1 wherein an array of fluid ~~volumes~~ samples, each having a known composition and known chemical and physical conditions and containing the moiety of interest for crystallization, is generated on the substrate surface.

Claim 6 (Amended): The method of claim 5 ~~1~~ wherein the moiety of interest for crystallization is ~~solubilized~~ stabilized by the ~~a~~ surfactant or chaotropic agent.

Claim 8 (Amended): The method of claim 1 ~~or 4~~ wherein the moiety of interest for crystallization is stabilized in a specific conformation by a ligand.

Claim 10 (Amended): The method of claim 9 ~~4 wherein the moiety of interest for crystallization comprises a biomacromolecule,~~ wherein the biomacromolecule is stabilized in a specific conformation by a ligand selected from the group consisting of ions, non-polymeric molecules, and biopolymers.

Claim 14 (Amended): The method of claim 6 wherein the moiety of interest comprises a biomacromolecule ~~, and the surfactant or chaotropic agent that solubilizes the biomacromolecule is a crystallization-promoting agent~~.

Claim 15 (Amended): The method of claim 9 ~~1, 2, 3, 6, or 10~~ wherein the ~~moiety of interest comprises a~~ biomacromolecule comprises ~~comprising~~ a partially or fully native protein domain.

Claim 19 (Amended): The method of claim 15 ~~18~~ wherein the biomacromolecule additionally comprises a fully denatured protein domain.

Claim 21 (Amended): The method of claim 9 ~~10~~ wherein at least one of the reagent-containing fluid droplets deposited at the site contains a second biomacromolecule.

Claim 22 (Amended): The method of claim 6, 8, or 10 further comprising ~~means~~ a step for detecting whether the moiety of interest for crystallization has formed crystals.

Claim 25 (Twice amended): The method of claim ~~6~~ 3 wherein ~~an array of fluid volumes each having~~ each sample has a different known composition and different known chemical and physical condition ~~s is generated on the substrate surface~~.

Claim 28 (Twice amended): The method of claim 1 or 2 ~~1, 2, or 3~~ further comprising controlling the temperature of the substrate and the ambient temperature and pressure

surrounding the reagent-containing droplets and the fluid ~~volumes~~ samples.

Claim 33 (Amended): The method of claim 3 wherein at least one of the ~~reagent-containing~~ fluid samples ~~droplets deposited at the site~~ contains one or more crystallization promoting agents selected from the group consisting of inorganic salts, organic salts, organic non-polymeric molecules, and polymers.

Claim 40 (Twice amended): The method of claim 38 ~~39~~, wherein each fluid ~~volume~~ sample contains polyethylene glycol and dimethyl sulfoxide.

Claim 41 (Twice amended): The method of claim 1 wherein ~~the moiety of interest for crystallization is a biomacromolecule and both~~ the fluid samples ~~volume~~ and the reagent-containing droplets have a volume of up to about 1 microliter.

Claim 42 (Twice amended): The method of claim 41, wherein ~~the moiety of interest for crystallization is a biomacromolecule and~~ the fluid samples have ~~volume has~~ a volume of about 1 picoliter to 30 nanoliters and the reagent-containing droplets have a volume of about 0.1 picoliter to 10 nanoliters.

Claim 43 (Twice amended): A method for generating ~~a fluid volume~~ at least one fluid sample having a volume of no more than about 100 microliters on a substrate, the fluid ~~volume~~ sample containing a moiety of interest for crystallization and having a known composition, and determining whether the known composition in combination with known chemical and physical conditions favor crystallization of the moiety of interest, the method comprising the steps of:

(a) positioning an acoustic ejector in acoustic coupling relationship with a reservoir of fluid, and directing acoustic radiation from the ejector into the reservoir, thereby depositing one or more reagent-containing fluid droplets at a site on the ~~a~~ substrate surface, wherein at least one of the ejector and the reservoir is movable relative to the other, and at least one of the reagent-containing fluid droplets deposited at the site ~~containing~~ contains the moiety of interest for crystallization; and

(b) detecting the presence and quantity of crystalline material composed of the moiety of interest in the fluid ~~volume~~ sample at the site.

Claim 44 (Twice amended): The method of claim 43 further comprising:

(c) depositing by focused energy ejection one or more reagent-containing fluid droplets at a site on a substrate surface having ~~a fluid volume~~ at least one fluid sample previously

deposited at the site; and

(d) detecting for the presence and amount of crystals of the moiety of interest in the ~~fluid volume~~ at least one fluid sample at the site.

Claim 45 (Amended): The method of claim 44 wherein said detecting ~~of steps (b) and (d)~~ step further comprises periodic detection of the amount and size of crystals

Claim 46 (Twice amended): The method of claim 43, 44, or 45 wherein said detecting step is carried out acoustically.

Claim 47 (Twice amended): The method of claim 43 or 44 ~~46~~ wherein an array of fluid ~~volumes~~ samples, each having a known composition and a known chemical and physical conditions and containing the moiety of interest for crystallization, is ~~are~~ generated on the substrate surface.

Claim 49 (Amended): The method of claim 48 ~~47~~ wherein the crystallization-promoting agent is a surfactant or chaotropic agent.

Claim 50 (Twice amended): The method of claim 49 ~~43~~ wherein the moiety of interest for crystallization is ~~solubilized~~ stabilized by the ~~a~~ surfactant or chaotropic agent.

Claim 52 (Amended): The method of claim 43 ~~or 50~~ wherein the moiety of interest for crystallization is a biomacromolecule, the biomacromolecule being stabilized in a specific conformation by a ligand selected from the group consisting of ions, non-polymeric molecules, and biopolymers.

Claim 57 (Amended): The method of claim 56 wherein the ~~moiety of interest~~ biomacromolecule comprises a native protein.

Claim 61 (Amended): The method of claim 56 ~~59~~ wherein the biomacromolecule ~~moiety of interest~~ additionally comprises a fully denatured protein domain.

Claim 64 (Twice amended): The method of claim 63 ~~50~~ further comprising a step for detecting whether the polypeptide ~~of interest for crystallization~~ has formed crystals.

Claim 66 (Twice amended): The method of claim 64 ~~63 or 65~~ wherein said detecting step is carried out acoustically.

Claim 67 (Twice amended): The method of claim 43 ~~66~~ further comprising independently controlling the temperature of the substrate and the ambient temperature and pressure surrounding the reagent-containing droplets and the fluid ~~volumes~~ samples.

Claim 72 (Twice amended): The method of claim 71 further comprising independently controlling the temperature of the substrate and the ambient gas temperature and pressure surrounding the reagent-containing droplets and the fluid ~~volumes~~ samples.

Claim 75 (Twice amended): The method of claim 46 ~~72~~ wherein each fluid ~~volume~~ sample contains polyethylene glycol and dimethyl sulfoxide.

Claim 76 (Twice amended): The method of claim 43 or 47 ~~75~~ wherein the fluid ~~volume~~ samples ~~has a volume of about 1 picoliter to 30 nanoliters~~ and the reagent-containing droplets have a volume of ~~about 0.1 picoliter to 10 nanoliters~~ of up to about 1 microliter.

Claim 77 (Twice amended): The method of claim 76 ~~45~~ wherein ~~the moiety of interest for crystallization is a biomacromolecule and~~ the fluid samples have ~~volume has~~ a volume of about 1 picoliter to 30 nanoliters and the reagent-containing droplets have a volume of about 0.1 picoliter to 10 nanoliters.

Claim 78 (Twice amended): A method for generating ~~a fluid volume~~ at least one fluid sample having a volume of no more than about 100 microliters on a substrate, containing a biomacromolecule of interest for crystallization and having a known composition and known chemical and physical conditions, comprising

positioning an acoustic ejector in acoustic coupling relationship with a reservoir of fluid, and

directing acoustic radiation from the ejector into the reservoir, thereby acoustically depositing one or more reagent-containing fluid droplets at a site on the ~~a~~ substrate surface,

wherein at least one of the ejector and the reservoir is movable relative to the other, and at least one of the reagent-containing fluid droplets deposited at the site contains the biomacromolecule of interest for crystallization.

Claim 79 (Amended): The method of claim 78 further comprising a step for detecting whether the biomacromolecule of interest for crystallization has formed crystals.

Claim 80 (Twice amended): The method of claim 78 wherein an array of fluid ~~volumes~~ samples, each having a known composition and known chemical and physical conditions and containing the biomacromolecule of interest for crystallization, is generated on the substrate surface.

Claim 81 (Amended): The method of claim 78 or 80 wherein at least one of the reagent-

containing fluid droplets deposited at the site contains one or more crystallization promoting agents selected from the group consisting of inorganic salts, organic salts, organic non-polymeric molecules, and polymers.

Claim 83 (Amended): The method of claim 81 wherein the biomacromolecule of interest for crystallization is ~~solubilized~~ stabilized by the ~~a~~ surfactant or chaotropic agent.

Claim 84 (Amended): The method of claim 81 ~~or 83~~ wherein the biomacromolecule of interest for crystallization is stabilized in a specific conformation by a ligand selected from the group consisting of ions, non-polymeric molecules, and biopolymers.

Claim 92 (Amended): The method of claim 89 ~~78~~ wherein the biomacromolecule of interest comprises a partially native protein domain.

Claim 93 (Amended): The method of claim 89 ~~92~~ wherein the biomacromolecule of interest additionally comprises a fully native protein domain.

Claim 94 (Amended): The method of claim 88 ~~92~~ wherein the biomacromolecule of interest additionally comprises a fully denatured protein domain.

Claim 99 (Twice amended): The method of claim 78 or 79 ~~or 80~~ further comprising controlling the temperature of the substrate and the ambient temperature and pressure surrounding the reagent-containing droplets and the fluid ~~volumes~~ samples.

Claim 109 (Twice amended): The method of claim 107 ~~106~~ wherein each fluid ~~volume~~ sample contains polyethylene glycol and dimethyl sulfoxide.

Claim 110 (Amended): The method of claim 78 ~~, 79,~~ or 80 wherein the biomacromolecule comprises a peptidic biopolymer selected from the group consisting of oligopeptides and polypeptides.

Claim 111 (Amended): The method of claim 78 ~~, 79,~~ or 80 wherein the biomacromolecule comprises a nucleotidic biopolymer selected from the group consisting of oligonucleotides and polynucleotides.

Claim 113 (Amended): The method of claim 78 wherein the fluid samples have ~~volume has~~ a volume of about 1 picoliter to 30 nanoliters and the reagent-containing droplets have a volume of about 0.1 picoliter to 10 nanoliters.

Claim 115 (Amended): The method of claim 114 wherein the immiscible phases comprise an aqueous fluid and a phospholipid and ~~the ejected droplets comprise~~ the biomacromolecule of

interest for crystallization is embedded or anchored in a phospholipid micelle or a phospholipid bilayer.

Claim 116 (Twice amended): A method for ejecting a different reagent-containing fluid from each of a plurality of fluid reservoirs toward designated sites on a substrate surface to form a combinatorial array of fluid ~~droplets~~ samples on the substrate, containing a biomacromolecule of interest for crystallization, the method comprising the steps of:

(a) positioning an acoustic ejector so as to be in acoustically coupled relationship to a first reservoir containing a first reagent-containing fluid;

(b) activating the ejector to generate acoustic radiation having a focal point near the surface of the first fluid, thereby ejecting a first droplet of the first reagent-containing fluid from the first reservoir toward a first designated site on the substrate surface, whereby the droplet adheres to the designated site;

(c) repositioning the ejector so as to alter the relative positions of the ejector and the first reservoir and to place the ejector in acoustically coupled relationship to a second reservoir containing a second reagent-containing fluid different from the first;

(d) activating the ejector as in step (b) to eject a second droplet of the second reagent-containing fluid from the second reservoir toward the first designated site on the substrate surface, whereby the second droplet adheres to the designated site and mixes with the first droplet;

(e) repeating steps (c) and (d) with additional reservoirs each containing a different reagent-containing fluid until the first designated site on the substrate surface has a fluid ~~volume~~ sample adhering thereto; and

(f) repeating steps (a) through (e) for the remaining designated sites of the array until each site has a fluid ~~volume~~ sample adhering thereto,

wherein each fluid ~~volume~~ sample contains the biomacromolecule of interest for crystallization ~~in the droplets of the reagent-containing fluid,~~ and each fluid ~~volume~~ sample occupying a designated site whereby the fluid ~~volumes~~ samples are arrayed on the substrate surface at the designated sites and the composition and chemical conditions at each site are known from the steps of the method and the reagent-containing fluids deposited.

Claim 117 (Twice amended): The method of claim 116 further comprising repeating steps (a)

through (f) to alter the composition of the fluid ~~volume~~ sample at each designated site.

Claim 118 (Twice amended): The method of claim 117 further comprising controlling the physical conditions of the substrate and ambient gas physical conditions surrounding the fluid droplets and the fluid ~~volumes~~ samples.

Claim 119 (Twice amended): The method of claim 118 wherein the physical conditions controlled are the temperature of the substrate and the ambient gas temperature and pressure ~~surrounding the fluid droplets and the fluid volumes~~.

Claim 123 (Amended): The method of claim 122 ~~116~~ wherein the immiscible phases comprise an aqueous fluid and a phospholipid and ~~the ejected droplets comprise~~ the biomacromolecule of interest for crystallization is embedded or anchored in a phospholipid micelle or a phospholipid bilayer.

Claim 129 (Amended): The system of claim 128 ~~126~~ wherein the means for ascertaining the quality of the crystals is by x-ray diffraction or scanning diffractometry.

The following is an examiner's statement of reasons for allowance: the examiner agrees with the Applicant's arguments that none of the prior art references discloses or fairly suggests the method or the system utilizing an acoustic ejector movable relative to the reservoir with a fluid to be ejected.

Claims 1-6, 7-12, 14-15, 19, 21-22, 25, 28, 33, 38, 40-50, 52-54, 56-57, 61, 63-64, 66-67, 70-72, 75-86, 88-94, 96, 99, 107 and 109-129 are allowed.

The new numbering of claims is 1 through 87.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh
4/23/04